

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

**In re application of:**

William J. Curatolo et al.

**Application No.** 09/770,562**Filed:** January 26, 2001**Confirmation No.** 8513For: SOLID PHARMACEUTICAL DISPERSIONS  
WITH ENHANCED BIOAVAILABILITY

Examiner: Blessing M. Fubara

Art Unit: 1613

**Attorney Reference No.** 8191-87018-01

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COMMISSIONER FOR PATENTS**DECLARATION OF RONALD A. BEYERINCK UNDER 37 CFR § 1.132**

RONALD A. BEYERINCK, being duly sworn does hereby declare and affirm the following:

1. That he received a Bachelor of Science degree in Biochemistry from University of California at Davis, in 1982 and a M.S. in Chemical Engineering, from Colorado State University in 1992; that he has 15 years of experience in solid pharmaceutical dispersion spray dry technologies.
2. That he is a Chemical Engineer at Bend Research, Inc., that he has been employed by Bend Research, Inc. for 19 years, and that he understands that Bend Research, Inc. is assignee of Application No. 09/770,562.
3. That scientists at Bend Research, during or around 1995 began development of solid spray-dried dispersion technology at Bend Research, Inc., with Mr. Beyerinck joining the team in early 1996, and at that date (at the start of such development) possessed the basic knowledge of one of ordinary skill in the art of solid dispersion technology which knowledge comprised forming dispersions of drugs and polymers using melting methods (also known as fusion methods), solvent methods (typically using slow evaporation or freeze drying techniques), and combinations of melting and solvent methods and that in circa 1997 there was little or no existing knowledge regarding spray dried solid dispersions or spray dried amorphous solid dispersions.

4. That he is an inventor and author on multiple patents, patent applications, and publications pertaining to spray dried solid dispersion technology (see Exhibit A listing certain of such patents, applications and publications).
5. That he has read Application No. 09/770,562 (hereinafter "the '562 Application") and the Examiner's Office Action dated August 26, 2011.
6. That he understands that the Examiner asserts that certain references disclose how to make "a spray dried solid dispersion (SDD) consisting of a sparingly water-soluble drug and hydroxypropyl methylcellulose acetate succinate (HPMCAS), the drug being molecularly dispersed and amorphous in the dispersion, and the dispersion is a homogeneous solid solution of the drug in the HPMCAS." That he has read these references, which are as follows:
  - EP 0 344 603 (Miyajima et al.)
  - EP 0 784 974 (Kigoshi et al.)
  - JP 57-176907 (Hikosaka)
  - 6,147,072 (Bymaster et al.)
  - Madhusoodanan et al., "Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series," *J. Clin. Psychiatry*, Abstract, Vol. 56, No. pp. 514-518 (Nov 1995).
7. That he disagrees with the Examiner's assertions that Miyajima, Kigoshi, Bymaster, Madhusoodanan and Hikosaka, alone or in combination with the knowledge of a person of ordinary skill in SDD technology in 1997, disclose to such person how to make the SDD claimed in the '562 Application.
8. That he believes he was a person of ordinary skill in the art of SDD technology prior to joining the development team in early 1996.
9. That in his opinion, a person of ordinary skill in the art at the effective filing date of the '562 Application, August 11, 1997, would have the following level of education and experience: education level of at least a bachelor of science (BS) in engineering, chemistry and/or pharmaceutical science and basic solid dispersion technology experience, but little or no knowledge or experience of spray-dried solid dispersion technology or spray-dried amorphous solid dispersion technology; that such persons in August of 1997 would not have had the knowledge necessary to produce the '562 Application claimed spray-dried solid dispersions,

which required knowledge or provided guidance as explained below, and obtaining such a SDD product would have taken extensive experimentation without predictability or a reasonable expectation of success.

10. That the information and/or guidance required to make or synthesize a spray dried solid dispersion consisting of a sparingly water-soluble drug and HPMCAS, the drug being molecularly dispersed and substantially completely amorphous in the dispersion, and the dispersion being a homogeneous solid solution of the drug in the HPMCAS, is not provided in any of the disclosures of the Paragraph 6 cited references, even when combined with the knowledge that one of ordinary skill in the art of SDD technology had available at the time of the '562 Application effective filing date, August 11, 1997, for at least the following reasons:
  - a. the cited references each only once mention spray drying and none include direction, instruction or other examples as to how to make any spray dried solid dispersion;
  - b. in 1997, prior to the invention disclosed in the '562 Application, it was not known that to make a completely or substantially completely amorphous spray dried solid dispersion as disclosed (described in Paragraph 6 above), it is necessary that the HPMCAS/drug-solution droplets be dried within a sufficiently short time period such that the drug in the dispersion droplets does not phase separate and/or crystallize and that such control of the dry time period is controlled through creating a suitably strong driving force for evaporation;
  - c. in 1997, prior to the invention disclosed in the '562 Application, it was not known that to make a completely or substantially completely amorphous spray dried solid dispersion as disclosed in the '562 Application (described in Paragraph 6 above), it is necessary that the HPMCAS/drug-solution droplets be dried sufficiently rapidly and completely such that the drug in the dispersion droplets do not phase separate and/or crystallize but instead forms substantially completely amorphous spray dried solid dispersion particles of drug and the dispersion polymer;
  - d. in 1997, to develop knowledge regarding how to make a completely or substantially completely amorphous HPMCAS/drug spray dried solid dispersion, Applicant had to experiment and develop a general technology applicable to a wide range of poorly soluble APIs, experiment and develop process knowledge of how to reliably produce solid dispersions, experiment and develop methods to assess the molecular state of the dispersion, e.g., PXRD, DSC, dissolution performance (*in vivo* and *in vitro*), and develop all such that a spray dried amorphous HPMCAS/drug solid dispersion would be physically stable;

- e. a skilled person attempting to make such a molecularly dispersed, homogeneous and substantially completely amorphous spray dried solid dispersion of HPMCAS/drug as claimed by Applicant, would need direction and guidance including, but not necessarily limited to, the following:
  - ✓ suitable solvents for a solution of drug and HPMCAS to make a spray dried solid dispersion
  - ✓ suitable temperatures for the drug, HPMCAS and solvent spray solution
  - ✓ suitable flow rate of the HPMCAS/drug solution to the spray drying chamber
  - ✓ suitable pressure in the spray drying chamber such that adequate process yields can be attained
  - ✓ suitable mixing of drying gases in the spray dry chamber
  - ✓ suitable temperatures for the mixing of drying gases in the spray dry chamber
  - ✓ suitable flow rates of drying gases into the drying chamber
  - ✓ suitable gas for the atomizer
  - ✓ suitable nozzle temperature for the atomizer
  - ✓ suitable flow rate of an atomizer gas
  - ✓ determination of the length of time the HPMCAS/drug solution droplets need in the chamber to achieve the required level of dryness
  - ✓ suitable HPMCAS/drug solution droplet size
  - ✓ suitable surface-to-volume ratio of the droplet
  - ✓ suitable final solvent content of the solid dispersion as it exits the dryer and conditions necessary to achieve such solvent content
- f. In August of 1997, when Applicant filed its first application, as discussed above, little or nothing was known in regard to how to reliably make spray dried amorphous solid dispersions and it was not known or predictable (there was no reasonable expectation of success) as to how to vary spray drying conditions to achieve a completely amorphous, molecularly dispersed HPMCAS/drug solid dispersion, and doing so took Applicant years of laboratory experimentation without knowing whether such could even be achieved;
- g. None of the required parameters or any guidance or even suggestions as to the necessary parameters is provided in any of the references;
- h. The importance of certain of the above parameters for spray drying HPMCAS/drug amorphous solid dispersions (that certain parameters were result effective) was not known in August of 1997 to those of ordinary skill in the art and determination of the

- above parameters required extensive and long-term trial and error analyses by the inventors of the '562 Application without predictability or an expectation of success;
- i. That he had personal knowledge that Bend Research, together with other scientists, evaluated several technologies for improving the bioavailability of low-solubility drugs, including spray drying, spray coating, spray agglomeration, spray precipitation, and milling. Based on initial studies, the spray drying process was selected due to its superior combination of improved bioavailability and improved physical stability, as well as its broad applicability;
  - j. That he had personal knowledge that it took at least 5 BRI research scientists and technicians at least 2 years to develop the spray-dry dispersion conditions and parameters to produce a SDD of HPMCAS/drug wherein the HPMCAS/drug was molecularly dispersed and completely amorphous in the SDD and the SDD was a homogeneous solid solution of the drug in the HPMCAS.
11. That he has reviewed the present application and believes there to be sufficient direction, guidance and examples in the specification such that one of ordinary skill in the art in August of 1997 could have made a spray dried solid dispersion consisting of a sparingly water-soluble drug and HPMCAS, the drug being molecularly dispersed and amorphous in the dispersion, having a drug/polymer weight ratio between 1:0.4 and 1:20, and the dispersion being a homogeneous solid solution of said drug in the HPMCAS with little or no experimentation, through reading Applicant's specification. That he has found particular guidance for making the same in the specification at, for example, p. 15, lines 16-19, p. 15, line 25 to p. 16, line 26, p. 21, line 23 to p. 24, line 9 and examples 15, 23, 1, 25, 26, 28 and 30.
12. That articles such as Chidavaenzi, "The use of thermal techniques to assess the impact of feed concentration on the amorphous content and polymorphic forms present in spray dried lactose" *International Journal of Pharmaceutics*, 159, pp. 67-74 (1997) (Exhibit B) illustrate how little was known in regard to spray drying completely amorphous solid dispersions in *circa* 1997. That Chidavaenzi, at about the same time Applicant filed its first application covering this invention, studied spray drying solid dispersions of lactose and attempted to determine whether feedstock concentration lead to products having different percentages amorphous contents. That Chidavaenzi reported many variables affect the form (amorphous or crystalline) of a spray dried product of lactose and that it might be in part based on solidification time but that he was not sure this was true. Specifically, Chidavaenzi stated that "The spray drying process is now better understood as a process that leads to loss of crystallinity in materials, possibly by a combination of rapid solidification of dissolved material and solid state transitions due to milling effects in the

atomiser." (Abstract - emphasis added.) That one can review Chidavaenzi's article for further illustration of how little was known in regard to spray dried solid dispersion technology in 1997, amorphous versus crystallinity of spray-dried products, and what parameters of spray drying caused such variety of amorphous percentage results, such as:

*The results for the feed containing 30 g/100 ml and the 40 g/100 ml (Table 2) samples were surprising as the measured amorphous content was higher than expected.* The 30 g/100 ml sample contained about 67% of the lactose in solution with the remainder in suspension. *It was expected that* the percentage amorphous values would reflect the percentage lactose that was in solution. The lactose in suspension was expected to emerge from the system as either a-monohydrate or anhydrous crystalline forms. *However, the 30 g/100 ml feed yielded a powder with 89% amorphous content, which was substantially higher than expected.* The 40 g/100 ml feed had approximately 50% of the lactose in solution and 50% in suspension. *However, the calculated value for amorphous content was 82%* which again is much higher than that which was dissolved in the feed material. *A possible explanation for the elevated amorphous contents of the suspension feeds is that atomisation pressure in the spray nozzle may have had a milling effect on the lactose that was in suspension. This pressure dependant milling effect may have resulted in the reduction of lactose particle size giving increased apparent solubility* (Buckton and Beezer, 1992), solubility would be further influenced by the change in temperature of the feed as it passes through the spray nozzle. *The effect of temperature in the nozzle affecting solubility is unlikely to be the only effect* as if this explanation was totally responsible for the changes in amorphous content, then the 20 g/100 ml sample would have been expected to be totally amorphous (as it was at equilibrium solubility at 25°C), whereas it remained at 91% amorphous. *It is however possible that changes in temperature in the nozzle become more significant when the suspended material load increases, perhaps due to particle-particle attrition.* *An alternative explanation* is that interparticle attrition and abrasion, under the influence of the atomiser centrifugal pressure, resulted in the physical disruption of the lactose crystal structure, giving a solid state transition to the amorphous form.

Pages 70-71, emphasis added to show the level of uncertainty and lack of predictability and understanding of spray-drying conditions and resulting percentages of amorphous versus crystalline products with in 1997.

13. Based on the foregoing facts and evidence it is my opinion that as one of ordinary skill in the art of spray dry technology in 1997, a person of ordinary skill in the art in August 1997 would not have been reasonably able to make the claimed molecularly dispersed, homogeneous and

amorphous spray dried solid HPMCAS/drug dispersions based on the basic knowledge available to me at that time and as disclosed in the references listed in Item 6 above, nor would the desired results have been predictable or reasonably expected.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at the place and date opposite the signature below.



Ronald A. Beyerinck

At Bend, Oregon  
(City and State)  
on this 23 day of November 2011.

## EXHIBIT A

### DECLARATION OF RONALD A. BEYERINCK UNDER 37 CFR § 1.132

#### **Patents**

Beyerinck, R.A., D.T. Smithey, W.K. Miller, M.M. Morgen, and C.J. Bloom, "Pharmaceutical Compositions Comprising Nanoparticles and Casein," U.S. patent pending, published as World Intellectual Property Organization Application No. WO 08/135852 (2008).

Beyerinck, R.A., C.J. Bloom, M.D. Crew, D.T. Friesen, M.M. Morgen, and D.T. Smithey, "Pharmaceutical Compositions Based on A) Nanoparticles Comprising Enteric Polymers and B) Casein," U.S. patent pending, published as World Intellectual Property Organization Application No. WO 08/065502 (2008).

Beyerinck, R.A., C.J. Bloom, M.D. Crew, D.T. Friesen, M.M. Morgen, and D.T. Smithey, "Pharmaceutical Compositions Comprising Enteric Polymers and Casein," U.S. patent pending, published as World Intellectual Property Organization Application No. WO 08/065506 (2008).

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Beyerinck, R.A., D.E. Dobry, D.T. Friesen, D.M. Settell, and R.J. Ray, "Spray-Drying Processes For Forming Solid Amorphous Dispersions Of Drugs And Polymers," U.S. patent pending, published as World Intellectual Patent Organization Application No. WO 05/011636 A1 (2005).

Beyerinck, R.A., D.E. Dobry, D.T. Friesen, R.J. Ray, and D.M. Settell, "Preparation of Pharmaceutical Composition Comprising Solid Amorphous Dispersion Comprising Drug and Polymer Involves Spraying Solution of Drug and Polymer to Form Droplets Having Specified Volume Average Size," U.S. patent pending, published as World Intellectual Property Organization Application No. WO 05/011636 (2005).

Curatolo, W.J., K.C. Waterman, A.G. Thombre, M.B. Fergione, M.C. Roy, L.E. Appel, D. Supplee, D.T. Friesen, M.B. Chidlaw, and R.A. Beyerinck, "Hydrogel-Driven Layered Drug Dosage Form," U.S. Patent No. 6,899,896 (2005).

Beyerinck, R.A., H.L.M. Deibebe, D.E. Dobry, R.J. Ray, D.M. Settell, and K.R. Spence, "Method for Making Spray-Dried Solid Amorphous Drug Dispersions Utilizing Modified Spray-Drying Apparatus," U.S. Patent No. 6,973,741 (2005).

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Beyerinck, R.A., R.J. Ray, D.E. Dobry, and D.M. Settell, "Method for Making Homogeneous Drug Dispersions Using Pressure Nozzles," U.S. patent pending, published as World Intellectual Property Organization Application No. WO 03/063821 A2 (2003).

Appel, L.E., W.C. Babcock, R.A. Beyerinck, M.B. Chidlaw, W.J. Curatolo, D.T. Friesen, S.M. Herbig, and A.G. Thombre, "Hydrogel-Driven Drug Dosage Forms," U.S. patent pending, published as World Intellectual Property Organization Application No. WO 02/11702 A2 (2002).

Appel, L.E., R.A. Beyerinck, M.B. Chidlaw, W.J. Curatolo, D.T. Friesen, K.L. Smith, and A.G. Thombre, "Hydrogel-Driven Drug Dosage Forms," U.S. patent pending, published as PCT International Application No. 20020015731 (2002).

Appel, L.E., R.A. Beyerinck, M.B. Chidlaw, W.J. Curatolo, D.T. Friesen, K.L. Smith, And A.G. Thombre, "Hydrogel-Driven Drug Dosage Forms Comprising Water-Swellable Compositions," U.S. patent pending, World Intellectual Property Organization Application No. WO 01/47500 A1 (2001).

Curatolo, W.J., M.B. Fergione, M.C. Roy, A.G. Thombre, K.C. Waterman, L.E. Appel, R.A. Beyerinck, M.B. Chidlaw, D.T. Friesen, and D. Supplee, "Hydrogel-Driven Layered Dosage Form for Controlled Release of Sertraline," U.S. patent pending, published as PCT International Application No. 20010044474 (2001).

Appel, L.E., D.T. Friesen, W.J. Curatolo, R.A. Beyerinck, J.A.S. Nightingale, and A.G. Thombre, "Matrix Controlled Release Device for a Low-Solubility Drug," U.S. patent pending, published as European Patent Application No. 2000-300546 (2000).

Appel, L.E., D.T. Friesen, W.J. Curatolo, R.A. Beyerinck, J.A.S. Nightingale, and A.G. Thombre, "Matrix Controlled Release Device for a Low-Solubility Drug," U.S. patent pending, published as European Patent Application No. 2000-300546 (2000).

## Publications

Morgen, M.M. , C.J. Bloom, R.A. Beyerinck, A. Bello, W. Song, K. Wilkinson, R. Steenwyk, and S. Shamblin, " Polymeric Nanoparticles for Increased Oral Bioavailability and Rapid Absorption Using Celecoxib as a Model of a Low-Solubility, High-Permeability Drug," *Pharm. Res.*, in press. Published on Springerlink.com on August 24, 2011, DOI: 10.1007/s11095-011-0558-7, pp. 1-14.

Dobry, Dan, Dana M. Settell, John M. Baumann, Rod J. Ray, Lisa J. Graham, and Ron. A. Beyerinck, "A Model-Based Methodology for Spray-Drying Process Development." *J. Pharm. Innovat.*, 4:3(2009)133-142.



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International Journal of Pharmaceutics 159 (1997) 67-74

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## The use of thermal techniques to assess the impact of feed concentration on the amorphous content and polymorphic forms present in spray dried lactose

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### Abstract

The influence of feed concentration (covering solutions and suspensions) on the physical forms of lactose obtained by spray drying was investigated. Isothermal microcalorimetry was used to assess the heats of crystallisation of the amorphous materials, which enabled the determination of the % amorphous content. Differential scanning calorimetry (DSC) provided qualitative data for the lactose polymorphs that were present in the spray dried products. Lactose monohydrate content was determined thermogravimetrically. The lactose which was dissolved was solidified as the amorphous form, due to the rapid drying conditions. The amorphous contents for the suspension feed concentrations were higher than the amount of lactose dissolved, which was due to a milling effect on the suspended lactose particles in the atomiser. The milling resulted in formation of amorphous material by solid state transition, or enhanced solubility or more likely a combination of both. Only the sample with the highest feed concentration contained small amounts of lactose monohydrate due to incomplete dehydration of the lactose in suspension. The presence of anhydrous lactose was due to the high inlet air temperatures causing dehydration of the lactose monohydrate which was in suspension. Variation of feed concentration during spray drying leads to products with different % amorphous contents and different proportions of crystalline forms. Beta lactose was not detected, either because it was absent or present in quantities below the detection limits of the thermal methods. The spray drying process is now better understood as a process that leads to loss of crystallinity in materials, possibly by a combination of rapid solidification of dissolved material and solid state transitions due to milling effects in the atomiser. © 1997 Elsevier Science B.V.

**Keywords:** Amorphous; Polymorphism; Lactose; Spray drying; Crystallisation; Microcalorimetry; Differential scanning calorimetry; Thermogravimetric analysis

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## 1. Introduction

### 1.1. Spray drying

Spray drying is a technique of importance in pharmaceutical industry, however the nature of the process is such that physical and chemical changes can occur in materials. The process involves the transformation of feed material from a fluid state into a dried particulate form by spraying the material into a drying air stream. Materials undergoing spray drying are processed via the following stages; atomisation of feed material, spray-air contact, drying of the spray material and separation of the material from the air stream. The process operational variables include; inlet air moisture, inlet temperature, feed rate, outlet temperature, air flow rate, feed concentration and atomisation pressure. A detailed description of spray drying is available elsewhere (Masters, 1990). Increasing the atomiser pressure creates smaller droplets at constant feed rate, resulting in high density fine particles. An increase in feed rate at constant operating conditions produces generally coarse spray particles and a wet product, due to inefficient drying. The nature of the spray dried product also depends on the properties of the feed material, where an increase in feed solids increases feed viscosity, which in turn produces coarse sprays on atomisation. An increase in feed solids usually results in an increase in particle size and bulk density. However, an increase in feed temperature may reduce feed viscosity causing a decrease in droplet size produced in the atomiser. This may improve atomisation efficiency of the process due to a slight reduction of the initial feed warm up period (Masters, 1990). The impact of feed concentration on the amorphous content and the different forms of the spray dried product, has seldom been studied in great detail. It is for this reason that this investigation was undertaken.

### 1.2. Characteristics of amorphous lactose

Pharmaceutical manufacturing techniques such as spray drying can produce materials in the amorphous state. Because the amorphous state is metastable with respect to the crystalline form,

phase transformations are likely to occur within the shelf life of the pharmaceutical product. These transformations usually result in loss of quality and potency in the product (Van Scoik and Carstensen, 1990).

Amorphous lactose produced by spray drying was found to have compaction properties which differed significantly from that of its crystalline forms (Vromans et al., 1986). Amorphous lactose is physically unstable above its glass transition temperature ( $T_g$ ) which is above most operating conditions. Numerous publications have demonstrated the physical instability of amorphous lactose at various relative humidities (e.g., Briggner et al., 1994; Buckton and Darcy, 1995, 1996; Sebhaut et al., 1993) due to the absorbed water plasticising the lactose such that  $T_g$  falls to or below room temperature. The critical relative humidity at which  $T_g$  falls below 25°C is quoted in most publications as around 48% RH. The effects of small quantities of moisture are not easily quantified; therefore, there is an uncertainty about the long term stability of amorphous lactose in pharmaceutical dosage forms. It was thought previously that glassy materials were stable below their glass transition temperature. However, molecular mobility at up to 50°C below the  $T_g$  of indomethacin, sucrose and polyvinyl pyrrolidone has been reported by Hancock et al., 1995. Such mobility may take place in amorphous lactose, which may have serious implications for the stability of products.

Although many studies have been undertaken on spray dried lactose, the impact of the feed concentration on the percentage amorphous content and the different lactose forms has been largely overlooked. It is thus the aim of this investigation to probe the effect of variation in feed concentration on the physical properties of the product.

## 2. Materials and methods

### 2.1. Materials

$\alpha$ -Lactose monohydrate (ex Smithkline Beecham, Great Burgh, Epsom, UK, batch E00131)

was used to prepare the spray dried samples and as a reference material for TGA, microcalorimetry and DSC experiments.  $\beta$ -lactose (Sigma, USA) was used in DSC experiments as a reference material.

## 2.2. Spray drying

Feed samples were prepared to give concentrations of 10 g/100 ml, 20 g/100 ml, 30 g/100 ml and 40 g/100 ml in distilled water. A Buchi 190 spray drier was used to prepare the samples from the different feed concentrations. The spray drying variables (Table 1), were kept constant, except for the feed rate which was varied for each feed concentration so as to minimise fluctuations in the outlet temperature.

The materials were collected and immediately desiccated over silica gel. The particle sizes of feed material and spray dried products were measured using laser diffraction (Malvern 2600C).

## 2.3. Isothermal microcalorimetry measurements

The microcalorimeter used was the 2277 Thermal Activity Monitor (TAM) (Thermometric AB, Sweden), which consisted of four independent channels. The technique has high sensitivity, being able to detect heat changes as small as  $10^{-6}\text{C}$ . The heat flow signal ( $dQ/dt$  in mW) is monitored as a function of time. Thus, by integrating the heat flow curves at a specific time, the heat evolved or absorbed can be obtained. Each sample was accurately weighed (approximately 20 mg) in a 3 ml glass ampoule, after which a tube containing a saturated solution of sodium chloride was added to give 75% RH at 25°C. The

**Table 1**  
Parameters used to spray dry lactose at different feed concentrations

Parameters	Controls
Air flow rate (dial setting)	12
Outlet temperature (°C)	85–90
Inlet temperature (°C)	185–190
Heating rate (dial setting)	11.5
Atomiser air flow rate (Normliter/h)	400

ampoules were sealed and temperature equilibrated for 30 min. A blank experiment was undertaken by sealing an identical ampoule and salt solution without powder present. The use of a freshly sealed blank ampoule minimises heat effects due to relaxation of the rubber stopper of the ampoule, evaporation from the salt solution and the baseline drift which is associated with environmental heat changes (Briggner et al., 1994). Experiments were carried out to investigate the percentage amorphous content in the spray dried samples by analysing the crystallisation peaks using the mean of at least three experimental runs.

## 2.4. Differential scanning calorimetry (DSC)

Differential Scanning Calorimeter (Perkin Elmer, DSC 7) was used to characterise the test samples and the reference material. The DSC sample weights were between 3.5 and 5.0 mg. Sealed aluminium pans were used and measurements were made in an atmosphere of nitrogen, with a heating rate of 20°C/min over a temperature range of 30–250°C. The instrument was calibrated using indium and the auto balance was also calibrated prior to weight measurements. At least three measurements were taken for each sample.

## 2.5. Thermogravimetric analysis (TGA)

Use of TGA (2950 Thermogravimetric Analyser, TA instruments) allowed the quantification of the lactose monohydrate content in the samples. This was achieved by analysing a derivative peak of the weight loss curve. The samples were heated over a temperature range of 30–250°C at a heating rate of 20°C/min. Four measurements for each sample were taken.

## 3. Results and discussion

A typical response of the spray dried material following exposure to 75% RH in the isothermal microcalorimeter is given in Fig. 1. The reference material,  $\alpha$ -lactose monohydrate was tested under

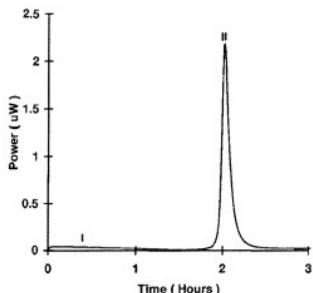


Fig. 1. A microcalorimetric trace showing an amorphous collapse peak (I) and a crystallisation peak (II) for spray dried lactose (20 g/100 ml) 20 mg at 75% RH, 25°C.

the same conditions and gave no crystallisation response, which confirmed that the material was 100% crystalline (best approximation). Two peaks are seen in Fig. 1, it was believed previously (e.g., Sebhater et al., 1993; Briggner et al., 1994) that the first peak represented the absorption of water vapour in the amorphous structure. However, recent developments in this area of study led to the view that the first peak is more likely a heat change due to the collapse of the amorphous structure (Buckton and Darcy, 1996). This recent notion is consistent with the opinion that vaporisation and absorption have an equal and opposite response, which cancel each other. The second peak is due to the crystallisation of the amorphous lactose. The shape of the second peak demonstrates that the crystallisation process is rapid and co-operative. This co-operative process proceeded after a critical moisture concentration was reached, which was sufficient to lower the glass transition temperature ( $T_g$ ) of amorphous lactose to below the operating temperature ( $T$ ). When the  $T_g$  of the materials was lowered to  $T$  or below, increased molecular mobility facilitated crystallisation.

It was expected that the materials spray dried from a 10 g/100 ml lactose solution would be totally amorphous, as rapid evaporation would cause fast solidification thus giving the material no opportunity to crystallise. A value of 50 mJ/mg (Fig. 2) was obtained by integrating the area under the crystallisation peak for this sample. This value is consistent with that obtained elsewhere for a totally amorphous lactose sample (Briggner et al., 1994), thus this sample is regarded as amorphous.

The material spray dried from a 20 g/100 ml feed sample (which is at the equilibrium solubility of lactose at 25°C), was found to contain 91% amorphous material (obtained from the ratio of the area of the crystallisation peak to that of the amorphous sample), which was within the expected range given the possibility that some nucleation sites may remain, as this solution is approximately at equilibrium solubility.

The results for the feed containing 30 g/100 ml and the 40 g/100 ml (Table 2) samples were surprising as the measured amorphous content was higher than expected. The 30 g/100 ml sample contained about 67% of the lactose in solution with the remainder in suspension. It was expected that the percentage amorphous values would reflect the percentage lactose that was in solution. The lactose in suspension was expected to emerge from the system as either  $\alpha$ -monohydrate or anhydrous crystalline forms. However, the 30 g/100 ml feed yielded a powder with 89% amorphous content, which was substantially higher than expected. The 40 g/100 ml feed had approximately 50% of the lactose in solution and 50% in suspension. However, the calculated value for amorphous content was 82% which again is much higher than that which was dissolved in the feed material. A possible explanation for the elevated amorphous contents of the suspension feeds is that atomisation pressure in the spray nozzle may have had a milling effect on the lactose that was in suspension. This pressure dependant milling effect may have resulted in the reduction of lactose particle size giving increased apparent solu-

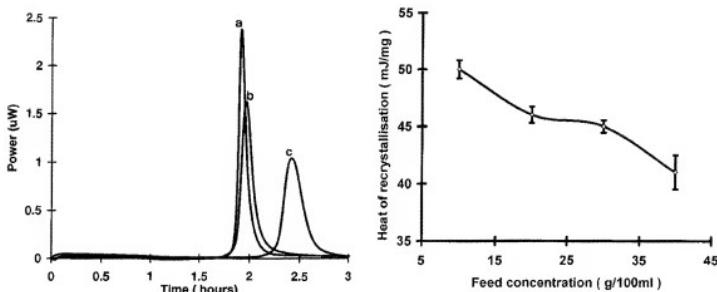


Fig. 2. (a) Typical microcalorimetric traces to show the crystallisation responses for the 40 g/100 ml (peak a), 20 g/100 ml (peak b) and 10 g/100 ml (peak c) products (30 g/100 ml trace not shown for clarity of the figure). Products with the highest amorphous content have the longest lag time prior to the crystallisation response, a plot of the mean area under the curve for each sample is given in (b). (b) A plot of mean area under the crystallisation curve (at 75%RH, 25°C) against feed concentration ( $n = 4$ , error bars represent standard deviations).

bility (Buckton and Beezer, 1992), solubility would be further influenced by the change in temperature of the feed as it passes through the spray nozzle. The effect of temperature in the nozzle affecting solubility is unlikely to be the only effect as if this explanation was totally responsible for the changes in amorphous content, then the 20 g/100 ml sample would have been expected to be totally amorphous (as it was at equilibrium solubility at 25°C), whereas it remained at 91% amorphous. It is however possible that changes in temperature in the nozzle become more significant when the suspended material load increases, perhaps due to particle-particle attrition. An alternative explanation is that inter-particle attrition and abrasion, under the influence of the atomiser centrifugal pressure, resulted in the physical disruption of the lactose crystal structure, giving a solid state transition to the amorphous form.

Changes in particle size were measured and are presented in Table 3. The feed material has a much larger size than any of the spray dried products. Based on these data some milling does take place during passage through the atomiser. The 10 g/100 ml feed produced the smallest size

product (Table 3) with the sizes for the products produced from other feeds being essentially identical (within experimental error). It can be concluded from these data that the presence of plentiful nucleation sites (which would be expected to exist in all except the 10 g/100 ml feeds) has resulted in larger particles, by allowing earlier solidification than for the material which was completely dissolved.

From the available evidence it is probable that a combination of the above explanations (solubility changes and solid state transitions) may be the reason for the unexpectedly high amorphous contents in the suspension feed products.

### 3.1. Determination of the lactose polymorphic forms present in spray dried lactose

The characterisation of polymorphs in the spray dried lactose samples was undertaken using DSC, TGA and microcalorimetry results.

From the isothermal microcalorimetry results it was established that a 10 g/100 ml sample contained 100% amorphous lactose, which meant that there was no crystalline material (best approximation) present. This observation was supported by

**Table 2**  
Summary of the feed material and the consequent nature of the spray dried product

Feed Conc. (g/100 ml)	% in solution in feed	Amorphous in product (%)	$\alpha$ -anhydrous in product (%)	Mono-hydrate in product (%)	$\beta$ -anhydrous in product (%)
10	100	100 (1.3)	0	0	0
20	ca. 100	91 (1.3)	9 (1.4)	0	0
30	67	89 (1.0)	11 (1.0)	0	0
40	50	82 (3.3)	13 (3.1)	5 (0.3)	0

The standard deviations are in parenthesis,  $n = 4$ .

The data for  $\beta$ -lactose are open to error as they are derived from the absence of a visible melt at the appropriate point on the DSC traces. It is reasonable to assume that a small part of the anhydrous material may indeed be present as  $\beta$ -lactose, but if this is so it is below the detection limit.

the DSC trace for this sample which showed no lactose monohydrate dehydration peak in the 140–150°C temperature range (see Fig. 3 for a DSC trace for reference material) and no  $\beta$ -lactose melting peak at about 235°C. The TGA derivative curve showed no evidence of weight loss associated with hydrate water. These data supported the isothermal microcalorimetry and as such it was concluded that the 10 g/100 ml samples contained no crystalline lactose.

The product from 20 g/100 ml feed contained 91% amorphous lactose, therefore the remaining 9% could potentially consist of one or all of the lactose polymorphs. The absence of any DSC melting peak at 235°C demonstrates that there are no detectable amounts of  $\beta$ -lactose in the sample.

The monohydrate dehydration peak was also absent, but there was a melting peak at 216°C (Fig. 3). The TGA derivative trace showed no weight loss associated with hydrate water, which indicated that there was no detectable lactose monohydrate in the sample. It is therefore, concluded that the 20 g/100 ml sample contained no lactose monohydrate and no  $\beta$ -lactose. By reasonable deduction, the 20 g/100 ml sample was thought to contain 9% anhydrous  $\alpha$ -lactose and 91% amorphous lactose. The observed DSC peak (Fig. 3) was in keeping with the literature value of 216°C for anhydrous lactose (Lerk, 1983). The 30 g/100 ml sample was found to contain 89% amorphous lactose and 11% anhydrous  $\alpha$ -lactose using a similar logic. It should be noted, however, that the absence of a melting peak on the DSC does not prove total absence of the  $\beta$ -lactose as there is a certain threshold quantity required to allow detection, as such the above estimates are best approximations.

The 40 g/100 ml sample, showed a TGA secondary weight loss derivative peak (see Fig. 4), which was consistent with the lactose monohydrate reference material. The derivative peak represented a loss of 0.0355 mg of water ( $0.0355 \times 10^{-3}/18$  moles of water). This number of moles was equivalent to the number of moles lactose monohydrate (1:1 molar ratio). The % lactose monohydrate content was then expressed as a % weight of the analysed sample. The lactose monohydrate content in the 40 g/100 ml sample was calculated to be approximately 5%. However, the dehydration peak was not visible on the DSC

**Table 3**

The particle sizes ( $\mu$ ) of the starting  $\alpha$ -lactose monohydrate and the spray dried products produced from different feed concentrations

	10% under-size	50% under-size	90% under-size
Starting material	9.2 (3.5)	22.8 (6.0)	46.0 (11.4)
10 g/100 ml feed	3.3 (0.6)	7.2 (0.3)	16.4 (5.0)
20 g/100 ml feed	3.4 (0.2)	11.2 (0.4)	23.5 (1.1)
30 g/100 ml feed	3.5 (0.3)	12.6 (1.0)	24.6 (1.7)
40 g/100 ml feed	3.8 (0.3)	13.9 (0.2)	25.9 (0.1)

Standard deviations are in parenthesis,  $n = 4$ .

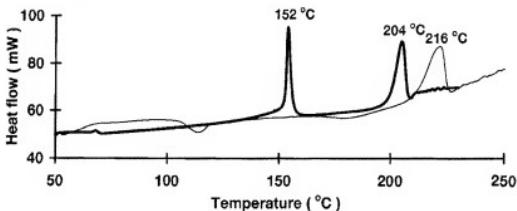


Fig. 3. A DSC trace for lactose monohydrate (reference material) showing a dehydration peak ( $152^{\circ}\text{C}$ ) and melting peak ( $204^{\circ}\text{C}$ ) (Bold line) and a typical scan for spray dried lactose ( $20\text{ g}/100\text{ ml}$ ) showing the absence of  $\beta$ -lactose melting peak and no lactose monohydrate dehydration peak (however a  $T_g$  is seen as a baseline disruption at ca  $120^{\circ}\text{C}$  and a melt at  $216^{\circ}\text{C}$  is observed).

trace for the sample, this may be due to the low sensitivity of the DSC to detect the presence of small amounts of lactose monohydrate (Angberg et al., 1991). The DSC trace for this material also showed no  $\beta$ -lactose melting peak and exhibited a melting peak at  $216^{\circ}\text{C}$ , which could represent the melting peak for either lactose monohydrate and anhydrous lactose. Based on the evidence available it is concluded that the material obtained from the  $40\text{ g}/100\text{ ml}$  feed consisted of 5% lactose monohydrate, 82% amorphous lactose and about 13% anhydrous lactose. The presence of lactose monohydrate in this sample may be due to the high feed rates which were necessary to control the outlet temperature. The feed rates for the

other samples were comparatively low, therefore, in the other samples it would have been easier for lactose to be dehydrated to form anhydrous lactose.

Whilst it should be remembered that the accuracy of the thermal analysis means that small amounts of other polymorphs will not have been detected, clear differences in the physical form are observed depending upon the feed concentration; these differences are summarised in Table 2. Substantial differences in product are possible depending upon both spray drying conditions and the concentration of the feed material.

#### 4. Conclusion

The concentration of feed material was found to have a significant effect on the properties of the spray dried materials. An increase in lactose content in the feed solution or suspension in the more concentrated preparations resulted in a decrease in percentage amorphous lactose in the spray dried products. Under the conditions used, the lactose in solution solidified in an amorphous state. However, at higher feed contents it was observed that suspended lactose was also converted from crystalline to amorphous material. Processes in the atomiser, followed by rapid solidification, cause the lactose in suspension to become amorphous through solid or liquid transitions or more likely a combination of both. At

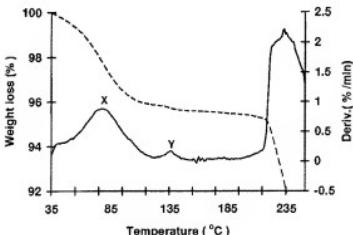


Fig. 4. TGA weight loss curve for spray dried lactose ( $40\text{ g}/100\text{ ml}$ ) showing a derivative peak corresponding to loss of absorbed ( $X$ ) and hydrate ( $Y$ ) water.

higher feed solids incomplete dehydration of the suspended lactose particles may occur, which may result in some lactose monohydrate in the products.

By selecting the appropriate feed concentrations spray dried lactose can be manufactured with various polymorphic proportions which suit the desired tabletting properties.

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